

(43) Date of publication: 14.07.2004 Bulletin 2004/29

(51) Int Cl.7: **A61N 1/365**

(21) Application number: 04250106.4

(22) Date of filing: 12.01.2004

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
 HU IE IT LI LU MC NL PT RO SE SI SK TR**
 Designated Extension States:
AL LT LV MK

(72) Inventors:

- Koh, Steve
South Pasadena CA 91030 (US)
- Park, Euljoon
Valencia CA 91381 (US)

(30) Priority: 10.01.2003 US 339989

(74) Representative: Rees, David Christopher et al
Kilburn & Strode
20 Red Lion Street
London WC1R 4PJ (GB)

(71) Applicant: Pacesetter, Inc.
Sylmar, CA 91342-9221 (US)

(54) System for detecting circadian states using an implantable medical device

(57) A system for detecting the circadian state of a patient using an implantable medical device based on selected blood carbon dioxide (CO_2) parameters. The implantable device tracks changes in end tidal CO_2 (etCO_2) levels and changes in maximum variations of pCO_2 levels per breathing cycle ($\Delta_{\text{cycle}}\text{CO}_2$) over the course of the day and determines the circadian state based thereon. Average etCO_2 levels are generally highest and average $\Delta_{\text{cycle}}\text{CO}_2$ levels are generally lowest while a patient is asleep and opposite while a patient is awake. Hence, by tracking changes in average etCO_2 and $\Delta_{\text{cycle}}\text{CO}_2$ levels over the course of the day, circadian states can be detected. Minute ventilation and activity levels are used to assist in the determination of the circadian state. Additional techniques are directed to detecting the stage of sleep.

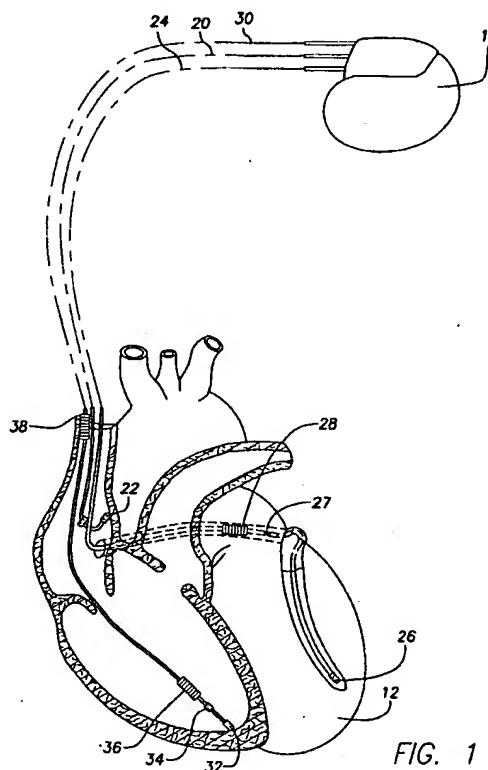


FIG. 1

Description

[0001] The invention relates generally implantable medical devices, such as pacemakers or implantable cardioverter/defibrillators (ICDs), and in particular to techniques for detecting circadian states (i.e. sleep/wake states) using an implantable medical device.

[0002] A pacemaker is a medical device for implant within a patient, which recognizes various arrhythmias such as an abnormally slow heart rate (bradycardia) or an abnormally fast heart rate (tachycardia) and delivers electrical pacing pulses to the heart in an effort to remedy the arrhythmias. An ICD is a device, also implantable into a patient, which additionally or alternatively recognizes atrial fibrillation (AF) or ventricular fibrillation (VF) and delivers electrical shocks to terminate fibrillation.

[0003] Pacemakers and ICDs are often provided with the capability to detect the circadian state of the patient, i.e. whether the patient is awake or asleep, and to adjust pacing parameters based on the circadian state. For example, a base pacing rate may be reduced while the patient is asleep then increased while the patient is awake. Conventionally, circadian state is detected based on time of day using an on-board clock or detected using a posture sensor. Typically, with an on-board clock, the patient is simply deemed to be awake during the day and during the evening but asleep at night. With a posture sensor, typically, the patient is deemed to be asleep while lying down. Neither technique is particularly effective. An on-board clock does not properly allow for a reduction in pacing rates if the patient sleep during the day or for an increase in pacing rates if the patient is awake at night. Posture detection does not properly distinguish between simply lying down rather than sleeping.

[0004] More sophisticated circadian state detection techniques have been developed that exploit patient activity levels detected using an activity sensor or that exploit minute ventilation detected using a thoracic impedance detector. A detailed description of an activity sensor for use in detecting circadian states is provided in U.S. Pat. No. 5,476,483, to *Bornzin et al.*, entitled "System and Method for Modulating the Base Rate During Sleep for a Rate-responsive Cardiac Pacemaker", which is incorporated herein by reference. Briefly, *Bornzin et al.* teaches the use of "activity variance" to determine if the patient is awake or sleeping. That is, an activity sensor has significantly less variability during sleep. Details of a system for exploiting minute ventilation in the detection of circadian states is set forth in U.S. Patent No. 6,128,534 to *Park et al.*, entitled "Implantable Cardiac Stimulation Device And Method For Varying Pacing Parameters To Mimic Circadian Cycles", which is also incorporated by reference herein.

[0005] By using activity variance or minute ventilation, many of the problems associated with conventional circadian state detection techniques are overcome. How-

ever, room for improvement remains. In particular, minute ventilation and activity-based detection techniques can be adversely affected by frequent movement of the patient while asleep, as can occur with patients who are restless sleepers or with patients with labored breathing while asleep. Congestive heart failure (CHF) patients suffering from severe Cheyne-Stokes respiration often have quite labored breathing while asleep causing both elevated minute ventilation levels and activity levels. Hence, techniques relying only on minute ventilation and/or activity levels can erroneously conclude the patient is awake instead of asleep.

[0006] Accordingly, it would be desirable to provide an improved technique for detecting circadian states and it is to this end that aspects of the invention are generally directed. In particular, the invention is generally directed to exploiting blood carbon dioxide (CO_2) parameters either alone or in combination with minute ventilation and activity levels for detecting circadian states. In this regard, it has been found that patients can tolerate a higher partial pressure of CO_2 (pCO_2) in the blood stream while asleep than while awake. Hence, average pCO_2 levels are generally higher, on the average, while asleep than while awake. Although still higher levels can be achieved while exercising, patients with pacemakers or ICDs typically do not exercise often enough to elevate average waking pCO_2 levels above average sleeping pCO_2 levels. Moreover, it is the increasing concentration of pCO_2 in the blood stream during the end tidal phase of the breathing cycle (also referred to herein as etCO_2) that ultimately triggers inhalation. Since patients tolerate a higher concentration of pCO_2 in the blood stream while asleep, etCO_2 is slightly higher, again on the average, while sleep than while awake. In addition, it has been found that, on the average, the difference between the minimum and maximum pCO_2 concentrations within individual breathing cycles (referred to herein as $\Delta_{\text{cycle}}\text{CO}_2$) is greater while awake than while asleep. Hence, these and other blood CO_2 -based parameters can be used to distinguish between sleeping and waking states, i.e. to detect circadian states, so that pacing control parameters can be adjusted accordingly.

[0007] At least one technique has been developed for detecting blood CO_2 levels using an implanted device. See U.S. Patent No. 4,716,887 to *Konig et al.*, entitled "Apparatus and Method for Adjusting Heart/Pacer Rate Relative to Cardiac PCO_2 to Obtain a Required Cardiac Output". With the technique of *Konig et al.*, average pCO_2 levels are detected and used in the adjustment of rate-responsive pacing rates under the assumption that higher pCO_2 levels generally correspond to a higher exercise states, thus requiring higher pacing rates. In other words, the technique detects changes in pCO_2 with time (ΔpCO_2) and adjusts pacing rates based on ΔpCO_2 . Although the assumption that higher pCO_2 levels generally correspond to a higher exercise states may be true while a patient is awake, this does not recognize the fact that average pCO_2 levels are actually higher while

asleep than while awake, at least for typical patients having pacemakers and ICDs. In any case, *Konig et al.* does not provide for the detection of circadian states based on blood CO₂ parameters but only for rate responsive pacing.

[0008] In accordance with one illustrative embodiment, a technique is provided for use with an implantable medical device for detecting the circadian state of the patient. The circadian state of the patient in which the device is implanted is detected by first detecting changes in selected blood CO₂ parameters and then determining the circadian state of the patient based upon the changes in the selected blood CO₂ parameters. Preferably, a pH/CO₂ sensor is used to track changes in etCO₂ levels as well as changes in $\Delta_{\text{cycle}}\text{CO}_2$. As noted above, it has been found that average etCO₂ levels are generally higher and average $\Delta_{\text{cycle}}\text{CO}_2$ levels are generally lower while a patient is asleep than while awake. Hence, by tracking changes in etCO₂ and $\Delta_{\text{cycle}}\text{CO}_2$ over the course of the day, circadian states can be detected. Alternatively, corresponding blood pH levels are tracked.

[0009] In an exemplary embodiment; wherein the implantable device is a pacemaker or ICD, various control parameters of the device are automatically adjusted based on the detected circadian state. For example, the device may be programmed to switch from a normal base pacing rate to a sleep base pacing rate when the patient falls asleep. Preferably, in addition to etCO₂ and $\Delta_{\text{cycle}}\text{CO}_2$, the implantable device also tracks minute ventilation using a thoracic impedance sensor and tracks activity levels using an accelerometer. Minute ventilation and activity levels are used to assist in the determination of the circadian state. However, by primarily basing the determination of circadian state on pCO₂ levels, the problems noted above that may arise when using only minute ventilation and/or activity levels are substantially avoided and a more reliable determination of the circadian state is achieved.

[0010] The invention also extends to the concept, in an implantable medical device for implant within a patient, of a method for detecting a circadian state of the patient, the method comprising: detecting changes in one or more blood carbon dioxide (CO₂) parameters; and determining the circadian state of the patient based upon the changes in the one or more blood CO₂ parameters.

[0011] Preferably, detecting changes in selected blood CO₂ parameters comprises detecting one or more of changes in end tidal CO₂ (etCO₂) levels and changes in maximum variation of pCO₂ level per breathing cycle ($\Delta_{\text{cycle}}\text{CO}_2$), and/or detecting one or more of changes in end tidal pH levels and changes in maximum variation of blood pH level per breathing cycle ($\Delta_{\text{cycle}}\text{pH}$).

[0012] Generally, determining the circadian state of the patient based upon the changes in the selected blood CO₂ parameters comprises identifying whether the patient is asleep or awake.

[0013] The method may further comprise detecting activity levels of the patient and the step of determining the circadian state of the patient additionally takes into account the detected activity levels. Alternatively, the method may further comprise detecting minute ventilation levels of the patient and the step of determining the circadian state of the patient additionally takes into account the detected minute ventilation levels; optionally the method may further comprise determining the ratio of minute ventilation to blood CO₂ levels of the patient and the step of determining the circadian state of the patient additionally takes into account this ratio. The method may further comprise determining a sleep stage of the patient based on the ratio of minute ventilation to blood CO₂ levels of the patient.

[0014] Preferably, detecting changes in selected blood CO₂ parameters is performed to detect changes in etCO₂ levels and changes in $\Delta_{\text{cycle}}\text{CO}_2$. The method may also include detecting activity levels of the patient and detecting minute ventilation levels of the patient and wherein the step of determining the circadian state of the patient takes into account a combination of $\Delta_{\text{cycle}}\text{CO}_2$ levels, etCO₂ levels, activity levels and minute ventilation levels. Preferably, determining the circadian state of the patient comprises generating a histogram representative of a range of values of the selected blood CO₂ parameters detected over a period of time and identifying the circadian state of the patient based upon the shape of the histogram. The method may also comprise controlling device functions based on the detected circadian state of the patient.

[0015] The invention also contemplates, in an implantable medical device for implant within a patient, a method for detecting a circadian state of the patient comprising: detecting blood carbon dioxide levels (pCO₂); detecting minute ventilation levels; determining a ratio of minute ventilation to pCO₂; and determining the circadian state of the patient based upon the ratio of minute ventilation to pCO₂.

[0016] The method may further comprise detecting end tidal pCO₂ levels of the patient and the step of determining the circadian state of the patient additionally takes into account the end tidal pCO₂ levels. The method may further comprise determining a sleep stage of the patient based on the ratio of minute ventilation to blood CO₂ levels of the patient.

[0017] Thus, various techniques are provided for detecting circadian states of a patient using an implantable device. Additional techniques are provided for determining the circadian state and/or the stage of sleep based on the ratio of minute ventilation to pCO₂. Other objects, features and advantages of the invention will be apparent from the detailed description to follow.

[0018] The above and further features, advantages and benefits of the present invention will be apparent upon consideration of the present description taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a simplified, partly cutaway view illustrating an implantable stimulation device in electrical communication with at least three leads implanted into a patient heart for delivering multi-chamber stimulation and shock therapy;

FIG. 2 is a functional block diagram of the multi-chamber implantable stimulation device of FIG. 2, illustrating the basic elements that provide cardioversion, defibrillation and/or pacing stimulation in four chambers of the heart and particularly illustrating a blood CO₂-based circadian state detection system for automatically detecting the circadian state of the patient;

FIG. 3 is a flow diagram illustrating a method performed by the circadian state detection system of FIG. 2 to determine circadian states;

FIG. 4 is a graph illustrating an individual breathing cycle and particularly illustrating the difference between sleeping and waking $\Delta_{\text{cycle}}\text{CO}_2$ levels and etCO₂ levels;

FIG. 5 is a graph illustrating a histogram employed by the circadian state detection system of FIG. 2 to determine circadian states;

FIG. 6 is a graph illustrating changes in $\Delta_{\text{cycle}}\text{CO}_2$, etCO₂, minute ventilation and activity levels over a period of twenty-four hours as a result of circadian cycles for a healthy patient;

FIG. 7 is a graph illustrating changes in $\Delta_{\text{cycle}}\text{CO}_2$, etCO₂, minute ventilation and activity levels over a period of twenty-four hours for a patient with CHF;

FIG. 8 is a graph illustrating changes in $\Delta_{\text{cycle}}\text{CO}_2$, etCO₂, minute ventilation and activity levels over a period of twenty-four hours for a patient who briefly awakens during the night;

FIG. 9 is a graph illustrating changes in $\Delta_{\text{cycle}}\text{CO}_2$, etCO₂, minute ventilation and activity levels over a period of two hours while awake for a patient who briefly exercises;

FIG. 10 is a graph illustrating minute ventilation vs. pCO₂ for various stages of sleep; and

FIG. 11 is a flow diagram illustrating an alternative method performed by the circadian state detection system of FIG. 2 to determine sleep stage as well as circadian state.

Stimulation Device

[0019] FIG. 1 illustrates a stimulation device 10 in electrical communication with a patient's heart 12 by way of three leads 20, 24 and 30 suitable for delivering multi-chamber stimulation and shock therapy. To sense atrial cardiac signals and to provide right atrial chamber stimulation therapy, the stimulation device 10 is coupled to an implantable right atrial lead 20 having at least an atrial tip electrode 22, which typically is implanted in the patient's right atrial appendage.

[0020] To sense left atrial and ventricular cardiac signals and to provide left-chamber pacing therapy, the

stimulation device 10 is coupled to a "coronary sinus" lead 24 designed for placement in the "coronary sinus region" via the coronary sinus so as to place a distal electrode adjacent to the left ventricle and additional electrode(s) adjacent to the left atrium. As used herein, the phrase "coronary sinus region" refers to the vasculature of the left ventricle, including any portion of the coronary sinus, great cardiac vein, left marginal vein, left posterior ventricular vein, middle cardiac vein, and/or small cardiac vein or any other cardiac vein accessible by the coronary sinus. Accordingly, the coronary sinus lead 24 is designed to receive atrial and ventricular cardiac signals and to deliver left ventricular pacing therapy using at least a left ventricular tip electrode 26, left atrial pacing therapy using at least a left atrial ring electrode 27, and shocking therapy using at least a left atrial coil electrode 28.

[0021] The stimulation device 10 is also shown in electrical communication with the patient's heart 12 by way of an implantable right ventricular lead 30 having, in this embodiment, a right ventricular tip electrode 32, a right ventricular ring electrode 34, a right ventricular (RV) coil electrode 36, and an SVC coil electrode 38. Typically, the right ventricular lead 30 is transvenously inserted into the heart 12 so as to place the right ventricular tip electrode 32 in the right ventricular apex so that the RV coil electrode 36 will be positioned in the right ventricle and the SVC coil electrode 38 will be positioned in the superior vena cava. Accordingly, the right ventricular lead 30 is capable of receiving cardiac signals, and delivering stimulation in the form of pacing and shock therapy to the right ventricle.

[0022] FIG. 2 illustrates a simplified block diagram of the multi-chamber implantable stimulation device 10 which is capable of treating both fast and slow arrhythmias with stimulation therapy, including cardioversion, defibrillation, and pacing stimulation. While a particular multi-chamber device is shown, this is for illustration purposes only and one of skill in the art could readily duplicate, eliminate or disable the appropriate circuitry in any desired combination to provide a device capable of treating the appropriate chamber(s) with cardioversion, defibrillation and/or pacing stimulation.

[0023] The stimulation device 10 includes a housing 40 which is often referred to as a "can", "case" or "case electrode", and which may be programmably selected to act as the return electrode for all "unipolar" modes. The housing 40 may further be used as a return electrode alone or in combination with one or more of the coil electrodes 28, 36 or 38, for shocking purposes. The housing 40 further includes a connector (not shown) having a plurality of terminals, 42, 44, 46, 48, 52, 54, 56 and 58 (shown schematically and, for convenience, the names of the electrodes to which they are connected are shown next to the terminals). As such, to achieve right atrial sensing and pacing, the connector includes at least a right atrial tip terminal 42 adapted for connection to the right atrial (A_R) tip electrode 22.

[0024] To achieve left chamber sensing, pacing and/or shocking, the connector includes at least a left ventricular (V_L) tip terminal 44, a left atrial (A_L) ring terminal 46, and a left atrial (A_L) shocking terminal (coil) 48, which are adapted for connection to the left ventricular tip electrode 26, the left atrial ring electrode 27, and the left atrial coil electrode 28, respectively.

[0025] To support right chamber sensing, pacing and/or shocking, the connector further includes a right ventricular (V_R) tip terminal 52, a right ventricular (V_R) ring terminal 54, a right ventricular (RV) shocking terminal (coil) 56, and an SVC shocking terminal (coil) 58, which are adapted for connection to the right ventricular tip electrode 32, right ventricular ring electrode 34, the RV coil electrode 36, and the SVC coil electrode 38, respectively.

[0026] At the core of the stimulation device 10 is a programmable microcontroller 60 that controls the various modes of stimulation therapy. As is well known in the art, the microcontroller 60 typically includes a microprocessor, or equivalent control circuitry or processor, designed specifically for controlling the delivery of stimulation therapy, and may further include RAM or ROM memory, logic and timing circuitry, state machine circuitry, and I/O circuitry. Typically, the microcontroller 60 includes the ability to process or monitor input signals (data) as controlled by program code stored in a designated block of memory. The details of the design and operation of the microcontroller 60 are not critical to the present invention. Rather, any suitable microcontroller 60 may be used that carries out the functions described herein. The use of microprocessor-based control circuits for performing timing and data analysis functions is well known in the art.

[0027] As shown in FIG. 2, an atrial pulse generator 70 and a ventricular pulse generator 72 generate pacing stimulation pulses for delivery by the right atrial lead 20, the right ventricular lead 30, and/or the coronary sinus lead 24 via a switch bank 74. It is understood that in order to provide stimulation therapy in each of the four chambers of the heart, the atrial pulse generator 70 and the ventricular pulse generator 72 may include dedicated, independent pulse generators, multiplexed pulse generators, or shared pulse generators. The atrial pulse generator 70 and the ventricular pulse generator 72 are controlled by the microcontroller 60 via appropriate control signals 76 and 78, respectively, to trigger or inhibit the stimulation pulses.

[0028] The microcontroller 60 further includes timing control circuitry 79 which is used to control the timing of such stimulation pulses (e.g., pacing rate, atrio-ventricular (AV) delay, atrial interconduction (A-A) delay, ventricular interconduction (V-V) delay, pacing mode, etc.), as well as to keep track of the timing of refractory periods, PVARP intervals, noise detection windows, evoked response windows, alert intervals, marker channel timing, etc.

[0029] The switch bank 74 includes a plurality of

switches for connecting the desired electrodes to the appropriate I/O circuits, thereby providing complete electrode programmability. Accordingly, the switch bank 74, in response to a control signal 80 from the microcontroller 60, determines the polarity of the stimulation pulses (e.g., unipolar, bipolar, combipolar, etc.) by selectively closing the appropriate combination of switches (not shown) as is known in the art.

[0030] Atrial sensing circuits 82 and ventricular sensing circuits 84 may also be selectively coupled to the right atrial lead 20, coronary sinus lead 24, and the right ventricular lead 30, through the switch bank 74, for detecting the presence of cardiac activity in each of the four chambers of the heart. Accordingly, the atrial and ventricular sensing circuits 82 and 84 may include dedicated sense amplifiers, multiplexed amplifiers, or shared amplifiers. The switch bank 74 determines the "sensing polarity" of the cardiac signal by selectively closing the appropriate switches. In this way, the clinician may program the sensing polarity independent of the stimulation polarity.

[0031] Each of the sensing circuits, 82 and 84, preferably employ one or more low power, precision amplifiers with programmable gain and/or automatic gain control, bandpass filtering, and a threshold detection circuit, to selectively sense the cardiac signal of interest. The automatic gain control enables the stimulation device 10 to deal effectively with the difficult problem of sensing the low amplitude signal characteristics of atrial or ventricular fibrillation.

[0032] The outputs of the atrial and ventricular sensing circuits 82 and 84 are connected to the microcontroller 60 for triggering or inhibiting the atrial and ventricular pulse generators 70 and 72, respectively, in a demand fashion, in response to the absence or presence of cardiac activity, respectively, in the appropriate chambers of the heart. The atrial and ventricular sensing circuits 82 and 84, in turn, receive control signals over signal lines 86 and 88 from the microcontroller 60, for controlling the gain, threshold, polarization charge removal circuitry (not shown), and the timing of any blocking circuitry (not shown) coupled to the inputs of the atrial and ventricular sensing circuits 82 and 84.

[0033] For arrhythmia detection, the stimulation device 10 utilizes the atrial and ventricular sensing circuits 82 and 84 to sense cardiac signals, for determining whether a rhythm is physiologic or pathologic. As used herein "sensing" is reserved for the noting of an electrical signal, and "detection" is the processing of these sensed signals and noting the presence of an arrhythmia. The timing intervals between sensed events (e.g., P-waves, R-waves, and depolarization signals associated with fibrillation which are sometimes referred to as "F-waves" or "Fib-waves") are then classified by the microcontroller 60 by comparing them to a predefined rate zone limit (e.g., bradycardia, normal, low rate VT, high rate VT, and fibrillation rate zones) and various other characteristics (e.g., sudden onset, stability, physiologic

sensors, and morphology, etc.) in order to determine the type of remedial therapy that is needed (e.g., bradycardia pacing, anti-tachycardia pacing, cardioversion shocks or defibrillation shocks, collectively referred to as "tiered therapy").

[0034] Cardiac signals are also applied to the inputs of an analog-to-digital (A/D) data acquisition system 90. The data acquisition system 90 is configured to acquire intracardiac electrogram signals, convert the raw analog data into digital signals and store the digital signals for later processing and/or telemetric transmission to an external device 102. The data acquisition system 90 is coupled to the right atrial lead 20, the coronary sinus lead 24, and the right ventricular lead 30 through the switch bank 74 to sample cardiac signals across any pair of desired electrodes.

[0035] Advantageously, the data acquisition system 90 may be coupled to the microcontroller 60 or other detection circuitry, for detecting an evoked response from the heart 12 in response to an applied stimulus, thereby aiding in the detection of "capture". Capture occurs when an electrical stimulus applied to the heart is of sufficient energy to depolarize the cardiac tissue, thereby causing the heart muscle to contract. The microcontroller 60 detects a depolarization signal during a window following a stimulation pulse, the presence of which indicates that capture has occurred. The microcontroller 60 enables capture detection by triggering the ventricular pulse generator 72 to generate a stimulation pulse, starting a capture detection window using the timing circuitry within the microcontroller 60, and enabling the data acquisition system 90 via control signal 92 to sample the cardiac signal that falls in the capture detection window and, based on the amplitude of the sampled cardiac signal, determines if capture has occurred.

[0036] The microcontroller 60 is further coupled to a memory 94 by a suitable data/address bus 96, where the programmable operating parameters used by the microcontroller 60 are stored and modified, as required, in order to customize the operation of the stimulation device 10 to suit the needs of a particular patient. Such operating parameters define, for example, pacing pulse amplitude, pulse duration, electrode polarity, rate, sensitivity, automatic features, arrhythmia detection criteria, pacing mode, and the amplitude, waveshape and vector of each shocking pulse to be delivered to the patient's heart 12 within each respective tier of therapy. A feature of the stimulation device 10 is the ability to sense and store a relatively large amount of data (e.g., from the data acquisition system 90), which data may then be used for subsequent analysis to guide the programming of the stimulation device 10.

[0037] Advantageously, the operating parameters of the stimulation device 10 may be non-invasively programmed into the memory 94 through a telemetry circuit 100 in telemetric communication with the external device 102, such as a programmer, transtelephonic transceiver or a diagnostic system analyzer. The telemetry

circuit 100 is activated by the microcontroller 60 by a control signal 106. The telemetry circuit 100 advantageously allows intracardiac electrograms and status information relating to the operation of the stimulation device 10 (as contained in the microcontroller 60 or memory 94) to be sent to the external device 102 through an established communication link 104.

[0038] The microcontroller includes a CO₂-based circadian state detection system 101 detecting the current circadian state of the patient and for controlling to operations of the pacemaker based thereon. Briefly, the circadian state detection system detects the circadian state based upon a combination of end tidal pCO₂ levels, $\Delta_{\text{cycle}}\text{CO}_2$ levels, minute ventilation levels and activity levels. To detect pCO₂ levels, the device uses a blood pH/CO₂ sensor 103, which derives pCO₂ levels from blood pH. Activity level and minute ventilation are detected using, respectively, an activity sensor 105 and a minute ventilation sensor 107. The activity sensor detects activity using any variety of techniques such as analyzing accelerometer signals. Furthermore, activity signals may be processed to generate an activity variance value in accordance with the techniques described in the aforementioned *Bornzin et al.* and *Park et al.* patents. The device may also include an additional physiologic sensor denoted 108 for detecting changes in cardiac output or changes in the physiological condition of the heart. The microcontroller 60 responds to signals received from the various sensors and from the circadian state detection system by adjusting various pacing parameters (such as base rate, pacing rate, AV Delay, V-V Delay, etc.) with which the atrial and ventricular pulse generators, 70 and 72, generate stimulation pulses. Although sensors 103, 105 and 107 are shown as being external to the device, depending upon the implementations, all or some of the components of the sensors may be internal to the device.

[0039] For a description of a blood pH sensor for detecting pCO₂ levels, see the aforementioned *Konig et al.* patent. A minute ventilation sensor is described in U.S. Patent No. 5,836,988 to *Cooper, et al.* Details regarding an exemplary activity sensor are provided in U.S. Patent No. 5,496,352 to *Renger*. As noted, descriptions of activity variance sensors are provided in the *Bornzin et al.* and *Park et al.* patents. Each of these patents is incorporated by reference herein.

[0040] The operation of the circadian state detection system is described in detail below with reference to FIGS. 3 - 9.

[0041] The stimulation device 10 additionally includes a power source such as a battery 110 that provides operating power to all the circuits shown in FIG. 2. For the stimulation device 10, which employs shocking therapy, the battery 110 must be capable of operating at low current drains for long periods of time and also be capable of providing high-current pulses (for capacitor charging) when the patient requires a shock pulse. The battery 110 must preferably have a predictable discharge charac-

teristic so that elective replacement time can be detected. Accordingly, the stimulation device 10 can employ lithium/silver vanadium oxide batteries.

[0042] The stimulation device 10 further includes a magnet detection circuitry (not shown), coupled to the microcontroller 60. The purpose of the magnet detection circuitry is to detect when a magnet is placed over the stimulation device 10, which magnet may be used by a clinician to perform various test functions of the stimulation device 10 and/or to signal the microcontroller 60 that an external programmer 102 is in place to receive or transmit data to the microcontroller 60 through the telemetry circuit 100.

[0043] As further shown in FIG. 2, the stimulation device 10 is shown as having an impedance measuring circuit 112 which is enabled by the microcontroller 60 via a control signal 114. Certain applications for an impedance measuring circuit 112 include, but are not limited to, lead impedance surveillance during the acute and chronic phases for proper lead positioning or dislodgment; detecting operable electrodes and automatically switching to an operable pair if dislodgment occurs; measuring respiration or minute ventilation; measuring thoracic impedance for determining shock thresholds; detecting when the device has been implanted; measuring stroke volume; and detecting the opening of the valves, etc. The impedance measuring circuit 112 is advantageously coupled to the switch bank 74 so that any desired electrode may be used.

[0044] It is a primary function of the stimulation device 10 to operate as an implantable cardioverter/defibrillator (ICD) device. That is, it must detect the occurrence of an arrhythmia, and automatically apply an appropriate electrical shock therapy to the heart aimed at terminating the detected arrhythmia. To this end, the microcontroller 60 further controls a shocking circuit 116 by way of a control signal 118. The shocking circuit 116 generates shocking pulses of low (up to 0.5 joules), moderate (0.5-10 joules), or high (11-40 joules) energy, as controlled by the microcontroller 60. Such shocking pulses are applied to the patient's heart through at least two shocking electrodes, as shown in this embodiment, selected from the left atrial coil electrode 28, the RV coil electrode 36, and/or the SVC coil electrode 38 (FIG. 1). As noted above, the housing 40 may act as an active electrode in combination with the RV electrode 36, or as part of a split electrical vector using the SVC coil electrode 38 or the left atrial coil electrode 28 (e.g., using the RV electrode as a common electrode).

[0045] Cardioversion shocks are generally considered to be of low to moderate energy level (so as to minimize pain felt by the patient), and/or synchronized with an R-wave, and/or pertaining to the treatment of tachycardia. Defibrillation shocks are generally of moderate to high energy level (i.e., corresponding to thresholds in the range of 5-40 joules), delivered asynchronously (since R-waves may be too disorganized) and pertaining exclusively to the treatment of fibrillation. Accord-

ly, the microcontroller 60 is capable of controlling the synchronous or asynchronous delivery of the shocking pulses.

[0046] In the remaining figures, flow charts are provided for illustrating the operation and novel features of various exemplary embodiments of the invention. In the flow chart, various algorithmic steps are summarized in individual "blocks". Such blocks describe specific actions or decisions to be made or carried out as the algorithm proceeds. Where a microcontroller (or equivalent) is employed, the flow charts presented herein provide the basis for a "control program" that may be used by such a microcontroller (or equivalent) to effectuate the desired control of the device. Those skilled in the art may readily write such a control program based on the flow charts and other descriptions presented herein.

Determination of Circadian State

[0047] Referring now to FIG. 3, the operation of the circadian state detection system of 101 of FIG. 2 will be described. Beginning at step 200, the detection system inputs signals from the pH/CO₂ sensor, the activity sensor and the minute ventilation sensor (sensors 103, 105 and 107 of FIG. 2, respectively.) The pH/CO₂ sensor converts detected blood pH levels into signals representative of pCO₂ levels before forwarding the information to the circadian state detection system, which detects the circadian state based, in part, on changes in pCO₂ levels. In the alternative, the pH/CO₂ sensor instead forwards signals representative of blood pH levels directly to the circadian state detection system, which detects the circadian state based on changes in blood pH levels. In the following, the invention is described with respect to the embodiment wherein blood pH levels are converted to pCO₂ levels before further processing. Detection of the circadian state directly using pH levels is essentially the same as set forth in the following descriptions but modified to reflect the fact that pH levels are numerically lower when pCO₂ levels are numerically higher and vice versa. This is simply because higher acidity is represented by a numerically lower pH. Since higher pCO₂ levels make the blood more acidic, the blood pH level is thereby numerically lower.

[0048] In any case, at step 202, the detection system identifies individual breathing cycles based in changes in pCO₂ levels. In this regard, pCO₂ varies from a maximum to a minimum during a single breathing cycle. Hence, a single breathing cycle can be detected by identifying consecutive peak maxima or minima in the pCO₂ signals. Alternatively, breathing cycles can be detected based on an analysis of minute ventilation signals. At step 204, the detection system then determines the maximum variation in the pCO₂ level within the latest breathing cycle, referred to herein as $\Delta_{\text{cycle}} \text{CO}_2$. (Note that $\Delta_{\text{cycle}} \text{CO}_2$ differs from ΔCO_2 , which instead refers to a change in average pCO₂ levels from one period of time to another.) If pH levels are instead directly proc-

essed, then the detection system determines the maximum variation in the blood pH level within the latest breathing cycle, referred to herein as $\Delta_{\text{cycle}}\text{pH}$. In any case, at step 206, the detection system also determines the etCO_2 level (or end tidal pH level) within each breathing cycle.

[0049] $\Delta_{\text{cycle}}\text{CO}_2$ and etCO_2 are both illustrated in FIG. 4, which shows changes in pCO_2 levels during two consecutive breathing cycles. As can be seen, the pCO_2 level varies from a maximum end tidal level to a minimum level. Note that the shape of the graph provided in FIG. 4 is primarily representative of a capnographic waveform, i.e. a representation of respiration pCO_2 levels as detected using an external respiration monitor. The actual shape of changes in pCO_2 levels during a breathing cycle may differ somewhat. The capnographic waveform of FIG. 4 is provided as it illustrates the general cyclic change in pCO_2 levels during a breathing cycle. In any case, two separate graphs are illustrated in FIG. 4: graph 208, shown with a solid line, illustrates the change in pCO_2 level occurring while the patient is awake; graph 210, shown with a dashed line, illustrates the change in pCO_2 level while the patient is asleep. As can be seen, $\Delta_{\text{cycle}}\text{CO}_2$ while awake is greater than $\Delta_{\text{cycle}}\text{CO}_2$ while asleep. In addition, etCO_2 is somewhat greater while asleep, than while awake.

[0050] The $\Delta_{\text{cycle}}\text{CO}_2$ level is a greater while awake than while sleep principally because a person breathes more deeply while awake so as to increase metabolic oxygen (O_2) consumption. The shallower breathing that occurs while asleep results in lower metabolic O_2 consumption, and hence less CO_2 is eliminated. Accordingly, the pCO_2 level never reaches as low a level while asleep than while awake. EtCO_2 levels are generally higher while sleep than while awake because a person can tolerate a higher level of pCO_2 in the blood before a new inhalation is triggered. In other words, the pCO_2 threshold at which a new inhalation occurs is higher while asleep than while awake. Hence, both etCO_2 levels and $\Delta_{\text{cycle}}\text{CO}_2$ levels may be used as an indicator of the circadian state of the patient, i.e. as an indication of whether the patient is awake or asleep.

[0051] Finally, with regard to FIG. 4, waking cycle 208 and sleep cycle 210 are both shown as having the exact same frequency. In general, the frequency at which breathing occurs is generally lower while asleep than while awake. Sleeping and waking breathing cycles are shown in FIG. 4 as having the same frequency simply for clarity in illustrating the pertinent differences therebetween. In any case, regardless of any differences in the frequency of breathing, $\Delta_{\text{cycle}}\text{CO}_2$ levels are generally greater while awake than while asleep and etCO_2 levels are generally lower while awake than while asleep.

[0052] Returning to FIG. 3, at step 212, the detection system determines the current circadian state of the patient based upon a combination of $\Delta_{\text{cycle}}\text{CO}_2$, etCO_2 , minute ventilation and activity levels. Finally, at step

214, the detection system adjusts pacing parameters based upon the current circadian state. For example, the current base pacing rate may be reduced while the patient is deemed to be asleep. If the pacemaker is provided with separately programmable base rates and circadian rates, the detection system controls the pacemaker to switch from the base rate to the circadian rate whenever the detection system determines the patient has transitioned from a waking state to a sleeping state. In addition to controlling pacing parameters, the detection system may control diagnostic functions of the device to, for example, trigger various self-tests of the device while the patient is asleep, since such tests are more advantageously performed while the patient is asleep due to generally lower pacing rates and correspondingly lower demands on the power supply and processing capabilities of the implanted device. In general, any of a wide variety of adjustments to the operational parameters of the implanted device may be performed, at step 214, based on the circadian state and no attempt is made herein to describe all such possible operations.

[0053] As noted, at step 212, the detection system detects the current circadian state of the patient based upon a variety of parameters that generally vary with circadian state including some combination of $\Delta_{\text{cycle}}\text{CO}_2$, etCO_2 , minute ventilation and activity levels. In one example, the system combines the various circadian parameters together to yield a single value or "metric" representative of the current circadian state. For example, each of the individual circadian parameters may be normalized, then averaged together, to yield the metric. Of course, calculation of the metric takes into account that some parameters, such as $\Delta_{\text{cycle}}\text{CO}_2$, tend to be numerically greater while the patient is awake whereas others, such as etCO_2 tend to be numerically lower. Hence, the combined metric is not calculated by simply averaging raw data together. In any case, the metric is then compared against threshold values indicative of whether the patient is asleep or awake. Preferably, a running average is maintained over the last one hour of detected parameters.

[0054] In general, it is believed that CO_2 -based parameters provide a more reliable indication of circadian state than minute ventilation or activity. Accordingly, the metric, which represents a combination of all detected circadian parameters, preferably weights the CO_2 -based parameters (i.e. $\Delta_{\text{cycle}}\text{CO}_2$ and etCO_2) more heavily than minute ventilation and activity. In one specific example, the parameters associated with CO_2 levels are doubled as compared to the activity parameters and minute ventilation parameters prior to combining to yield the single metric. As can be appreciated, a wide variety of techniques may be employed for combining or blending the information received from various sensors into a single value that can be compared against predetermined threshold levels.

[0055] Insofar as the threshold levels are concerned,

in one example, a single upper threshold is employed and, if the combined metric exceeds the upper threshold, the patient is deemed to be awake. Likewise, a single lower threshold is employed and, if the combined metric falls below the lower threshold, the patient is deemed to be asleep. If the metric falls between the upper and lower threshold values, the system considers the circadian state to be currently ambiguous and hence makes no changes to operational parameters of the device. In other implementations, a single threshold is provided and the detection system identifies the current circadian state simply based upon whether the combined metric exceeds or falls below the single threshold value. In still other implementations, different threshold values may be employed depending upon whether the patient is currently in the sleep state or the waking state. In other words, once the patient is deemed to be asleep, a higher threshold must be surpassed before the detection system concludes that the patient has awoken and resets operational parameters of the implanted device. Likewise, once the patient is deemed to be awake, the metric must fall below a lower threshold before the detection system concludes that the patient has fallen asleep. Hence, once a detection system has identified the current circadian state, it is biased to remain within that state. This helps prevent frequent changes in operational parameters of the device in circumstances where in the parameters used to detect the circadian state yield generally ambiguous results.

[0056] An alternative technique for determining the circadian state, at step 212, is graphically represented in FIG. 5. The technique employs a three-dimensional histogram. In the specific example of FIG. 5, etCO_2 levels are detected then used to increment counters within a set of histogram bins. Each bin corresponds to a range of breath-by-breath etCO_2 levels. If the patient is asleep, bins indicative of relatively high etCO_2 levels are incremented more often than those indicative of low etCO_2 levels. While the patient is awake, the opposite occurs. Periodically, preferably once each hour, the detection system examines the counter values within each of the bins and determines the current circadian state based upon the relative shape of the resulting histogram or upon some value representing the average of the histogram values. Within FIG. 5, histogram 216 illustrates exemplary counter levels occurring while the patient is awake. Histogram 218 illustrates exemplary counter levels occurring while the patient is asleep. Additional histograms may be maintained for each of the parameters that have been detected. Alternatively, the aforementioned combined metric may be used to increment bins within a metric histogram. The centroid of each one hour's worth of histogram data may be calculated to summarize the trend in data such that each full histogram need not be stored for more than one hour thus saving memory. In any case, once the shape of the bins of the latest histogram has been examined and a determination of the current circadian state is made, the bins

are cleared. In still other implementations, fuzzy logic is employed to determine the current circadian state based upon relative the values of the various detected parameters.

[0057] Referring to the remaining figures, various examples will now be described. Within FIG. 6, variations in average minute ventilation, activity level, etCO_2 and $\Delta_{\text{cycle}}\text{CO}_2$ are shown over a period of twenty-four hours. As can be seen, while the patient is awake, minute ventilation, activity and $\Delta_{\text{cycle}}\text{CO}_2$ levels are generally higher than while asleep. EtCO_2 levels are generally lower while awake than while asleep. Hence, in the example FIG. 6, each of the parameters varies strongly with circadian state and any one of the parameters can be used to detect the circadian state. However, depending upon the particular patient, some of the individual parameters may vary in ways that are unexpected or ambiguous. For example, within FIG. 7, both minute ventilation and activity parameters vary generally randomly over the course of the day, perhaps as a result of labored breathing, such that circadian cycles cannot reliably be determined therefrom. However, both the etCO_2 and $\Delta_{\text{cycle}}\text{CO}_2$ levels vary strongly with circadian state. This is one reason why, preferably, the CO_2 -based parameters are weighted more heavily in the determination of the circadian state than either activity or minute ventilation. In the specific example of FIG. 7, the on-going variations in minute ventilation and activity may be the result of, for example, CHF.

[0058] FIG. 8 illustrates an example wherein a temporary change in $\Delta_{\text{cycle}}\text{CO}_2$ and etCO_2 levels occurs while patient is asleep. This may be the result of a period of somewhat deeper breathing while the patient is asleep. Because breathing is deeper, minute ventilation also increases temporarily. However, because patient is still asleep, activity remains at a low level. Hence, FIG. 8 illustrates the desirability of employing activity-based parameter along with the other parameters to help prevent a false detection of a change in circadian state. If blood CO_2 levels only were employed, the detection system might erroneously conclude that the patient has awoken.

[0059] FIG. 9, which covers only a period of two hours, illustrates a brief burst of exercise occurring while the patient is awake. As can be seen, minute ventilation, activity, etCO_2 and $\Delta_{\text{cycle}}\text{CO}_2$ levels all spike upwardly briefly. Hence, FIG. 9 illustrates that brief increases in etCO_2 levels should not be misconstrued as an indication of entry into a sleep state. By basing the detection of the circadian state on at least an hour worth of data, such misinterpretations are substantially avoided. As explained above, although exercise can raise etCO_2 levels temporarily, most patients with pacemakers or ICDs do not engage in enough exercise to elevate the average etCO_2 level while awake over the average etCO_2 level while asleep. Moreover, by factoring in activity and minute ventilation into the circadian state detection, false detections of sleep states are further

avoided.

[0060] Additionally, it has been found that blood CO_2 levels vary according to the stage of sleep. This is illustrated in FIG. 10, which shows minute ventilation values (V_E) as a function of pCO_2 levels for various sleep stages. As can be seen from the figure, the pCO_2 triggering point at which inhalation begins is lowest while awake, higher while in stage 3/4 sleep, still higher in stage 2 sleep, and highest in rapid-eye movement (REM) sleep. Since etCO_2 levels depend upon the pCO_2 concentration that triggers inhalation, etCO_2 levels likewise depend on the stage of sleep and so changes in etCO_2 levels while asleep can be used to detect the sleep stage. Also, note that the slope of minute ventilation as a function of pCO_2 varies according to sleep state, with the slope equal to 1.60 while awake, 0.81 while in stage 3/4 sleep, 0.69 while in stage 2 sleep and 0.45 while in REM sleep. Thus, implantable medical devices such as devices incorporating both chest impedance measuring devices and blood pH sensors can be configured to calculate the ratio or slope of minute ventilation to pCO_2 and to use the ratio to determine whether the patient is asleep or awake and, if asleep, to further determine the stage of sleep.

[0061] An exemplary technique for detecting circadian state and/or sleep stage based on the ratio of minute ventilation to pCO_2 is shown in FIG. 11. At steps 300 and 302, detection system 101 (FIG. 2) determines pCO_2 and minute ventilation based on signals received, respectively, from the pH/ CO_2 sensor and the minute ventilation sensor (also FIG. 2.) At step 304, the detection system determines the ratio or slope of minute ventilation to pCO_2 . This may be determined, for example, by averaging pCO_2 levels and minute ventilation levels over some period of time (such as the last fifteen minutes) then taking the numerical ratio of the two averaged values or by recording individual pairs of values of minute ventilation and pCO_2 and determining the slope. In any case, at step 306, the detection system also determines the average etCO_2 level (or end tidal pH level). Then, at step 308, the detection system determines the circadian state of the patient based upon either the average etCO_2 level or the average ratio of minute ventilation to pCO_2 or a combination of both. If the patient is asleep, the detection system further determines the stage of sleep, i.e. either REM, stage 2 or stage 3/4. Finally, at step 310, the detection system adjusts control parameters of the implanted device based upon the current circadian state and/or the current sleep stage.

[0062] For example, if the ratio of minute ventilation to pCO_2 is found, at step 308, to be greater than 1.0, the patient is deemed to be awake; otherwise, the patient is deemed to be asleep. If the ratio is found to be in the range of 0.75 to 1.0, the patient is deemed to be in stage 3/4 sleep. If the ratio is found to be in the range of 0.50 to 0.75, the patient is deemed to be in stage 2 sleep. If the ratio is found to be less than 0.50, the patient is deemed to be in REM sleep. These thresholds may be

calibrated for use with particular patients. Likewise, the average etCO_2 level can be compared against threshold values to determine the stage of sleep, with the appropriate threshold levels determined experimentally and calibrated, if needed, for use with particular patients. A metric can be generated that combines the ratio data and the etCO_2 data to determine the circadian state and/or sleep stage, with the ratio data and the etCO_2 data weighted relative to one another, as desired. Moreover, the ratio data can also be used to supplement the circadian state detection technique of FIG. 3., i.e. it can be combined with activity data, $\Delta_{\text{cycle}}\text{CO}_2$ data, etc.

[0063] Hence, analysis of blood CO_2 alone or in combination with minute ventilation may be used to distinguish stages of sleep and, if desired, operational parameters of the implantable medical device may be adjusted based upon sleep state. Although the examples provided herein primarily relate to implantable cardiac stimulation devices, principles of the invention may be employed within other implantable medical devices, such as neurostimulation devices, wherein the operation of the device may need to be controlled based upon the sleep state of the patient. The techniques invention are applicable in a wide variety of applications and no attempt made herein to enumerate all such applications.

Claims

1. A system for detecting the circadian state of a patient for use in an implantable medical device for implant within a patient, comprising:

means for detecting one or more blood carbon dioxide (CO_2) parameters;
means for identifying changes in the one or more blood CO_2 parameters over a plurality of breathing cycles; and
means for determining the circadian state of the patient based upon the changes in the one or more blood CO_2 parameters over the plurality of breathing cycles.

2. A system as claimed in Claim 1, characterised in that: the detecting means comprises:

a sensor system operative to detect blood carbon dioxide levels (pCO_2); and
the identifying and determining means comprises
a CO_2 -based circadian state detection system operative to detect maximum variations of pCO_2 levels occurring within individual breathing cycles ($\Delta_{\text{cycle}}\text{CO}_2$), track changes in $\Delta_{\text{cycle}}\text{CO}_2$, and determine the circadian state of the patient based upon the changes in $\Delta_{\text{cycle}}\text{CO}_2$.

3. A system as claimed in Claim 2, **characterised in that** the sensor system also comprises an activity sensor and a minute ventilation sensor, and the circadian state detection system is operative to determine the circadian state of the patient based on a combination of end tidal CO₂ (etCO₂) levels, $\Delta_{\text{cycle}}\text{CO}_2$, activity levels and minute ventilation levels. 5
4. A system as claimed in Claim 3 further comprising a controller operative to control device functions based on the detected circadian state of the patient. 10
5. An implantable medical device for implant within a patient, **characterised in that** it incorporates a system as claimed in any preceding Claim, for detecting the circadian state of a patient. 15
6. An implantable medical device for implant within a patient, **characterised by** a control system comprising: 20
- a blood CO₂ sensor;
 - an activity sensor;
 - a minute ventilation sensor; and
 - a controller operative to control device functions based on a combination of blood CO₂ parameters, activity levels and minute ventilation levels. 30

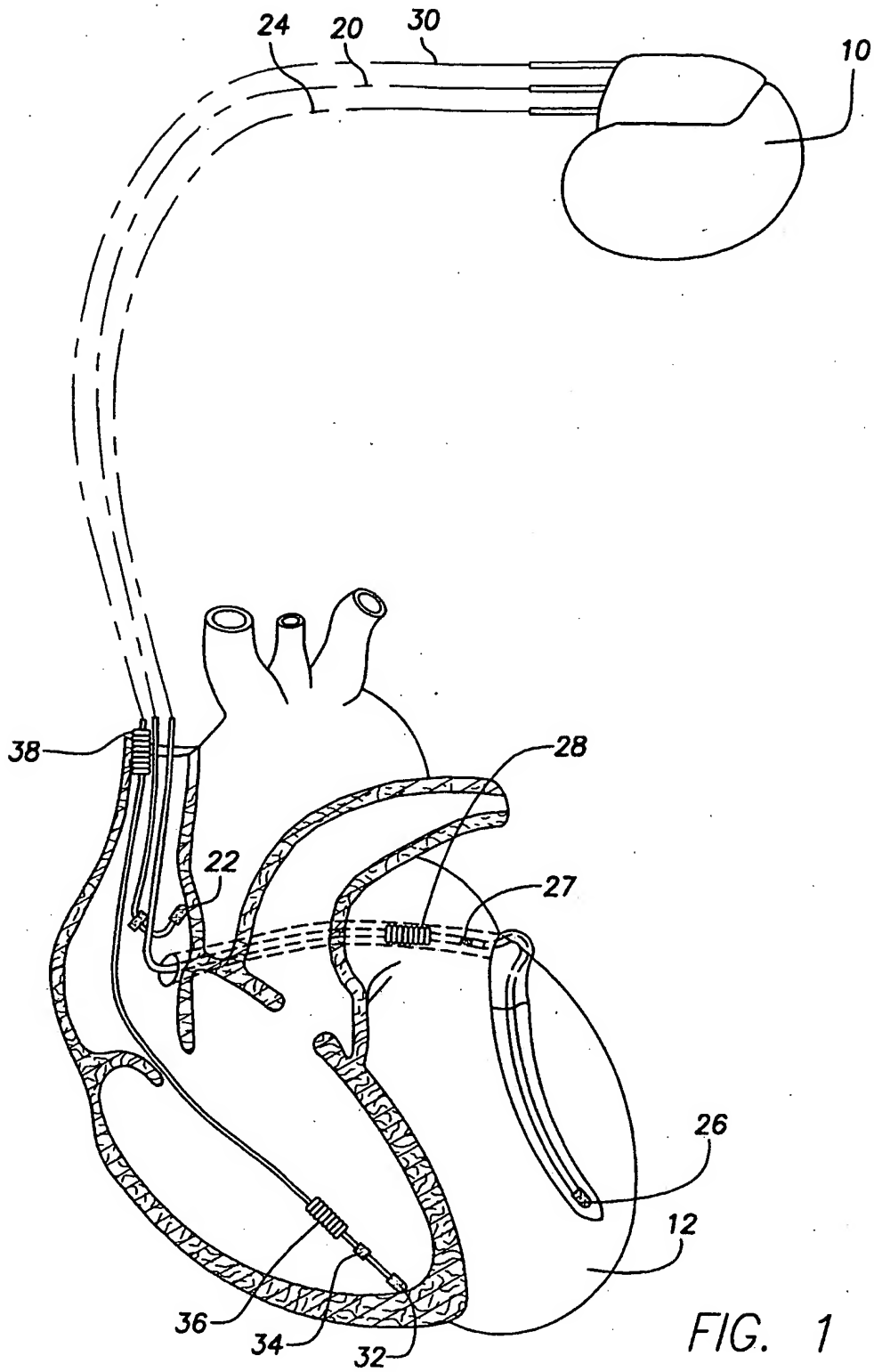
35

40

45

50

55



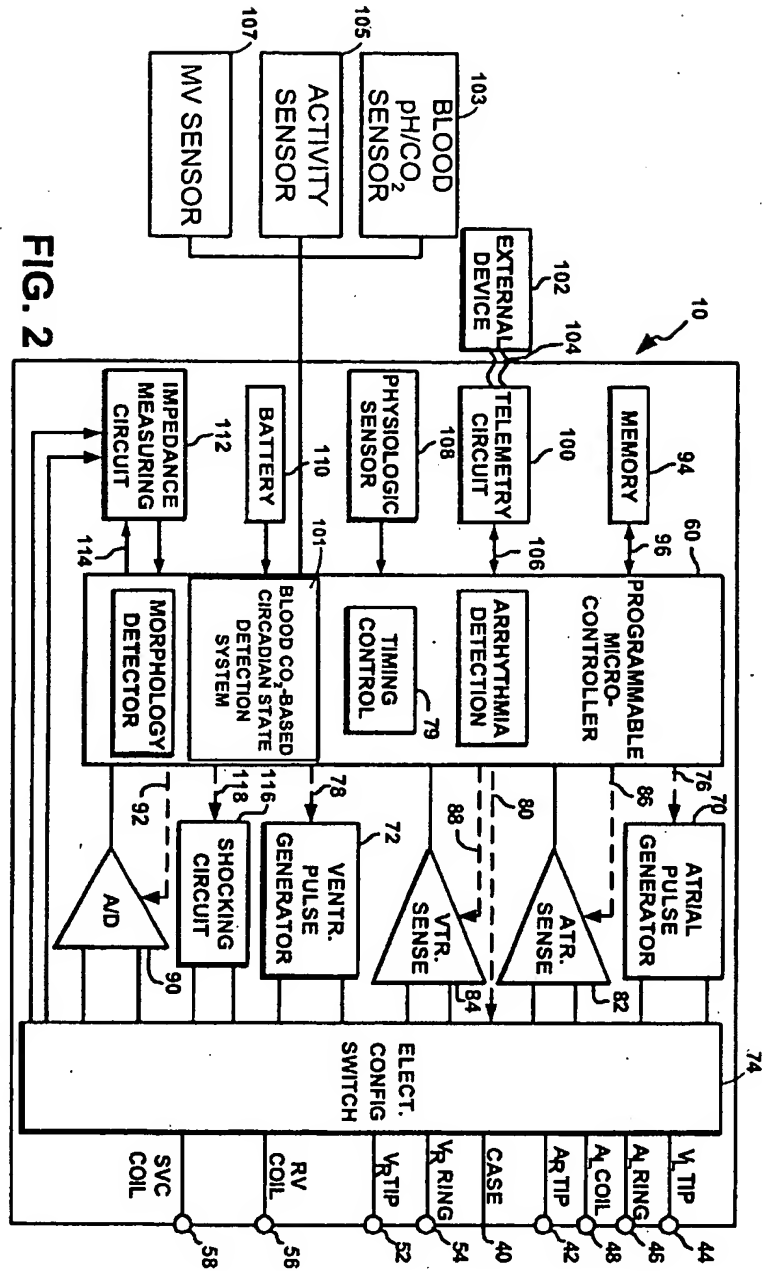


FIG. 2

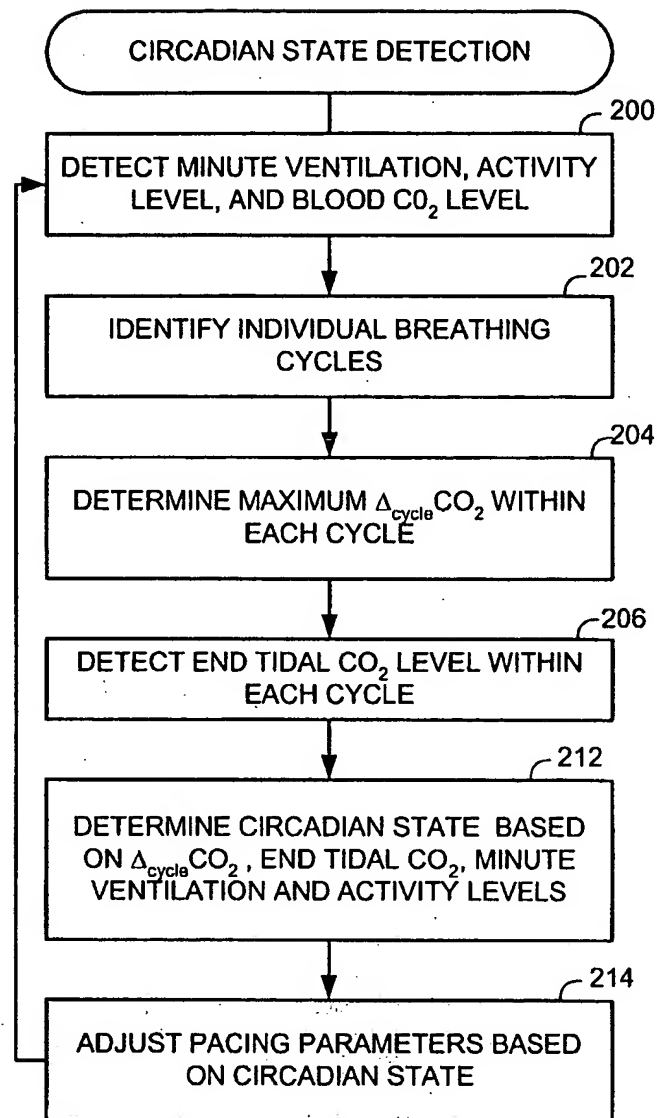


FIG. 3

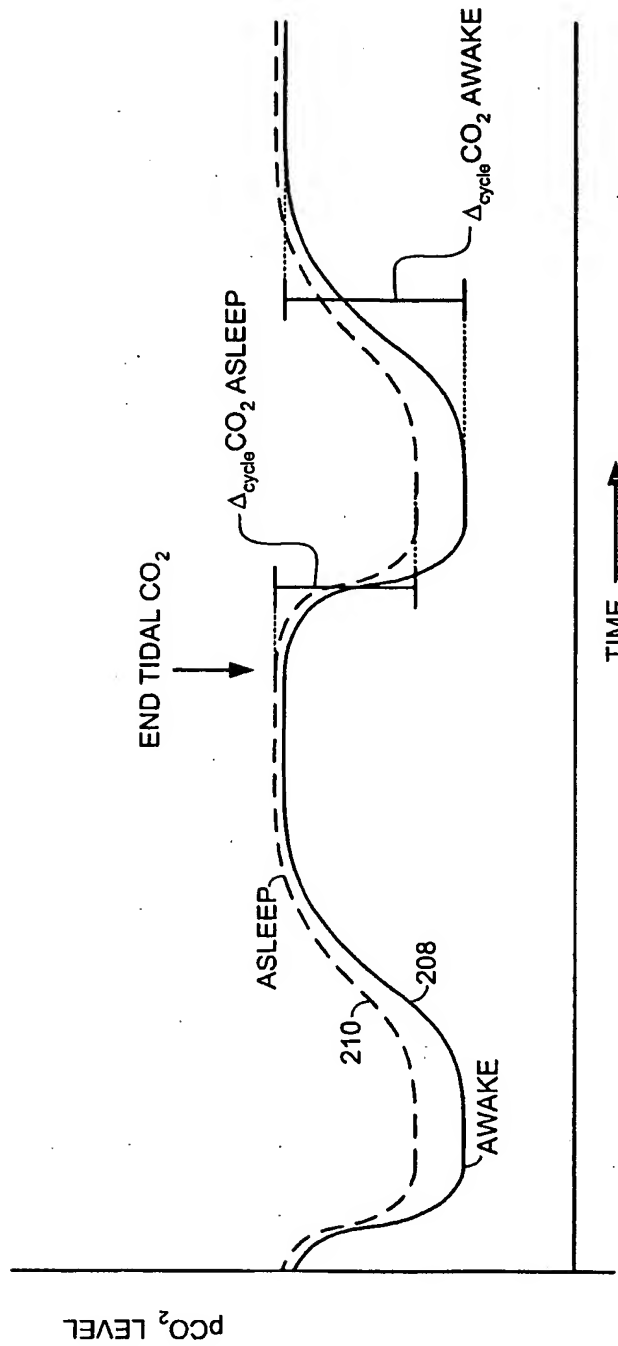


FIG. 4

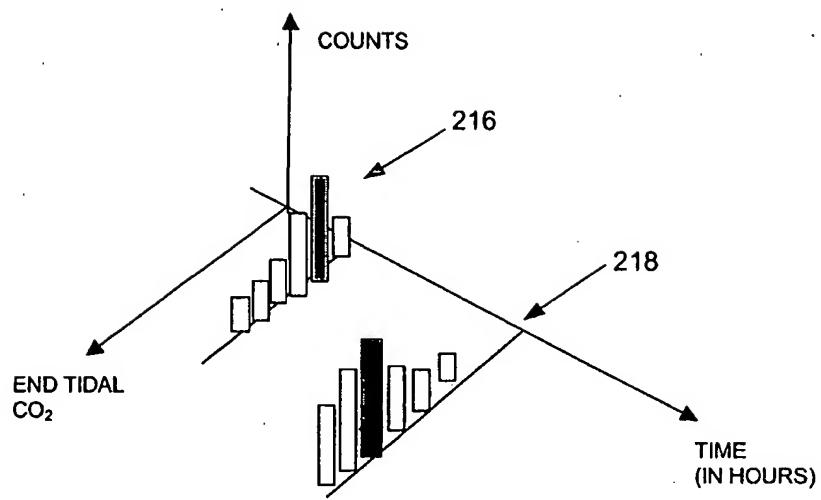
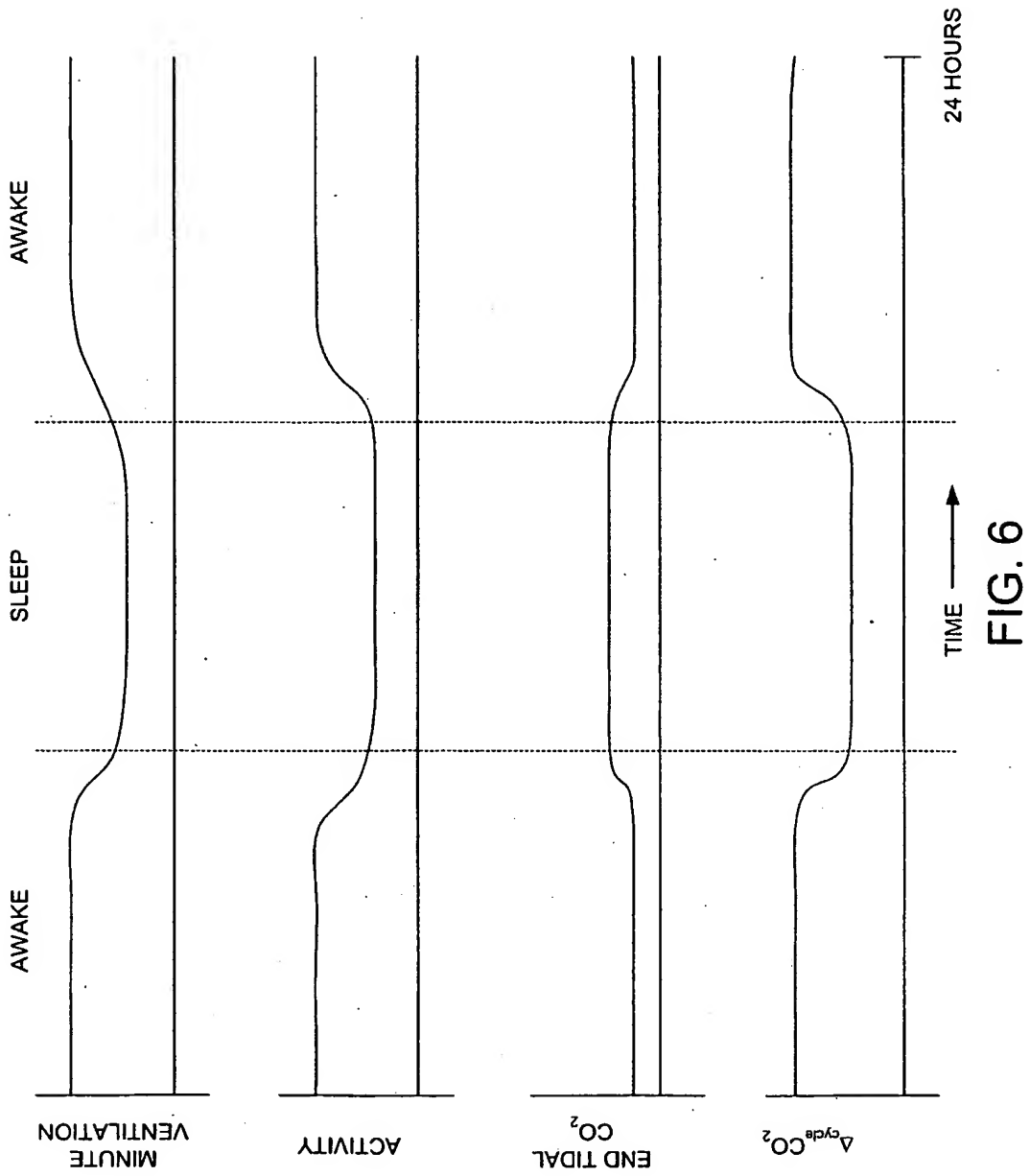
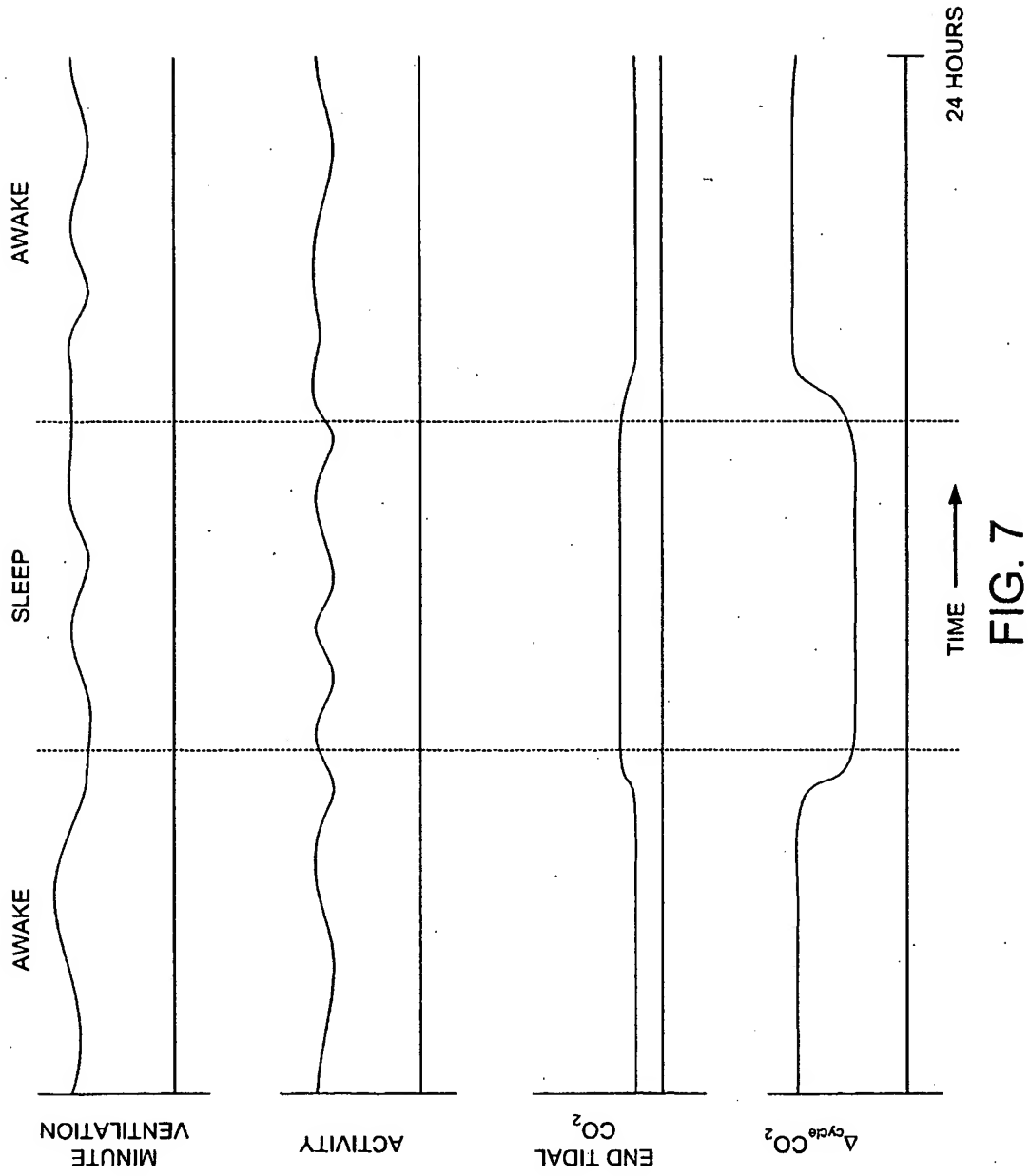
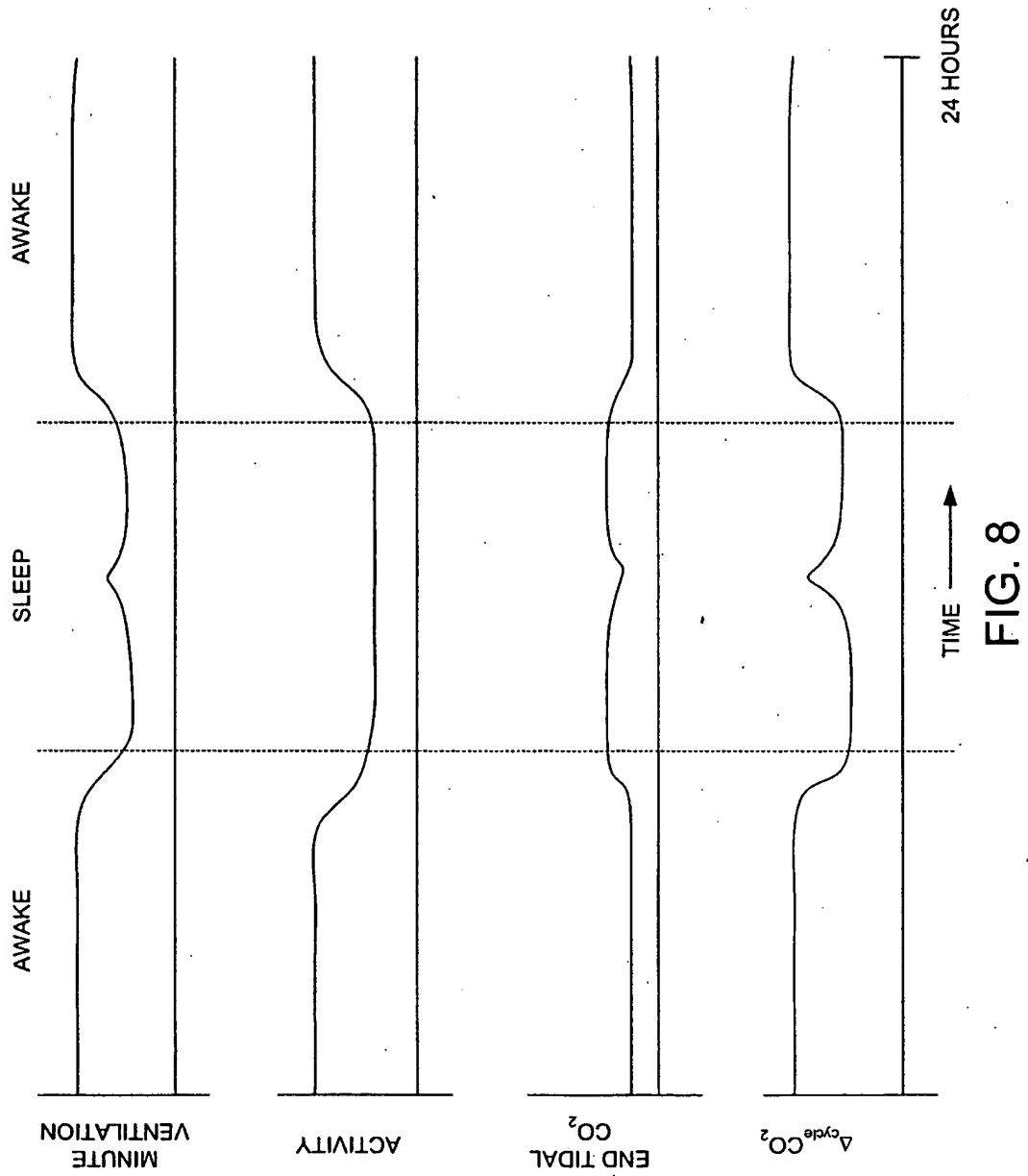


FIG. 5







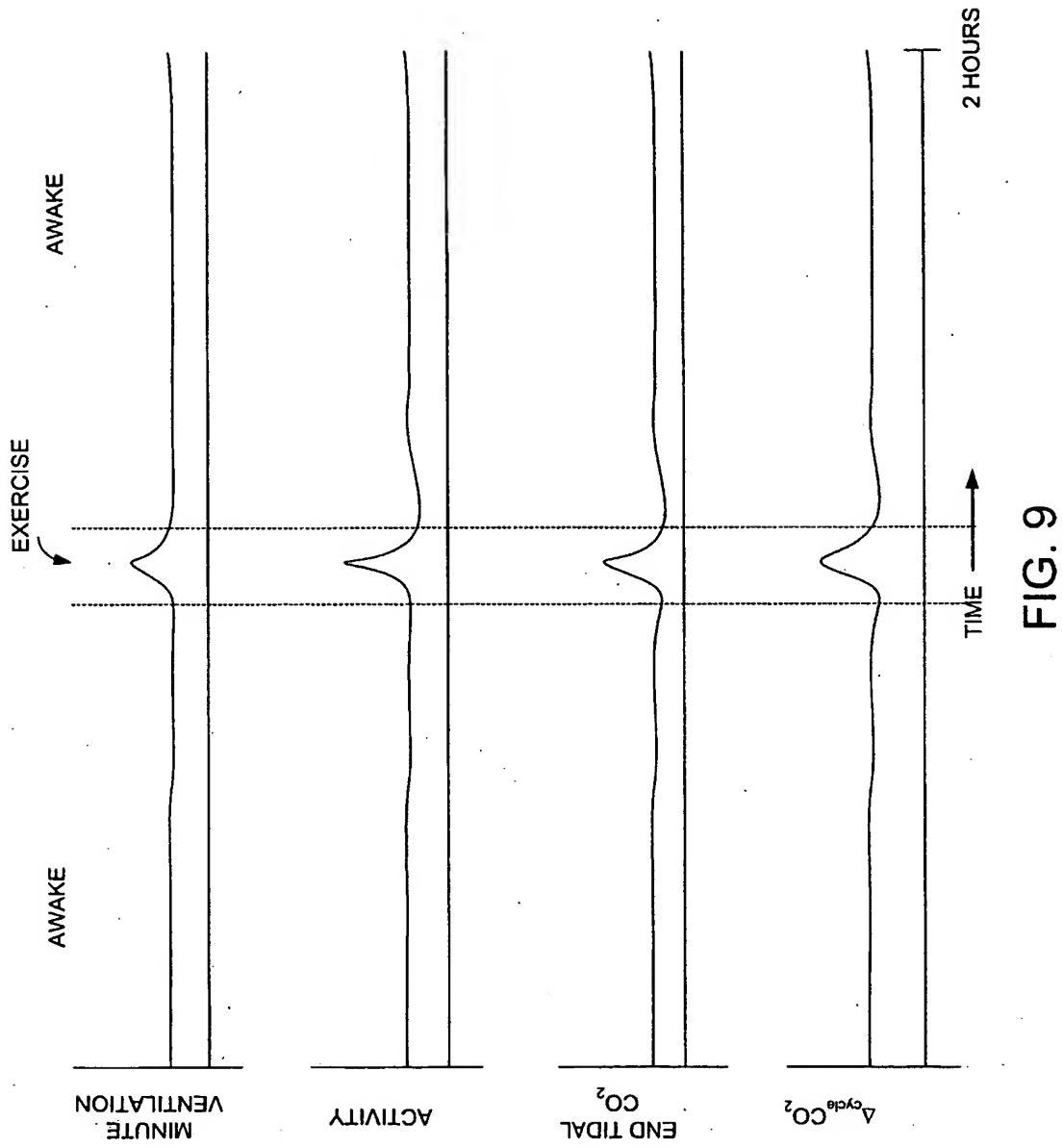


FIG. 9

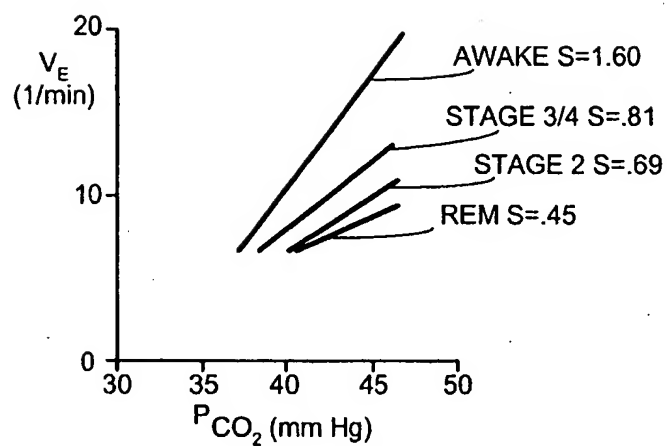


FIG. 10

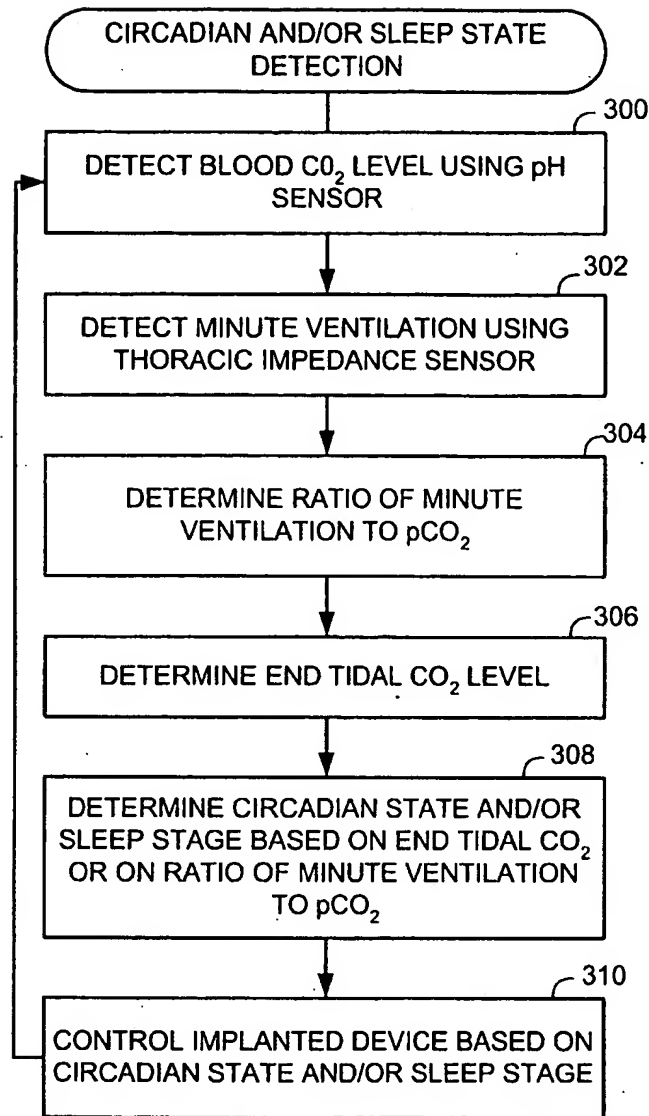


FIG. 11



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 04 25 0106

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 2002/052632 A1 (FENSTER MAIER ET AL) 2 May 2002 (2002-05-02) * paragraphs [0042],[0463] *	1,5,6	A61N1/365
A	---	2-4	
X	US 2002/032467 A1 (MIKA YIVAL ET AL) 14 March 2002 (2002-03-14) * paragraphs [0005],[0031] *	6	
X	US 6 055 454 A (HEEMELS JAN PIETER) 25 April 2000 (2000-04-25) * column 1, line 8-11,42-47 * * column 3, line 20-33 * * column 4, line 61,62 *	1,5,6	
A	---	2-4	
X	US 5 908 392 A (SLOMAN LAURENCE S ET AL) 1 June 1999 (1999-06-01) * column 1, line 7 * * column 3, line 7-9 * * column 6, line 50-60 *	6	
	---		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
P,X	US 2003/153953 A1 (KOH STEVE ET AL) 14 August 2003 (2003-08-14) * paragraphs [0026],[0042],[0050],[0057]-[0059] *	1,5,6	A61N A61B
P,X	US 2004/002741 A1 (WEINBERG LISA P) 1 January 2004 (2004-01-01) * paragraphs [0001],[0009],[0010],[0055],[0099] *	1,5,6	

The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 29 March 2004	Examiner Aronsson, F
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : Intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 03.02 (PUB/COI)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 04 25 0106

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29-03-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002052632 A1	02-05-2002	IL 116699 A	13-09-2001
		US 6330476 B1	11-12-2001
		US 6317631 B1	13-11-2001
		AU 715925 B2	10-02-2000
		AU 1170197 A	01-08-1997
		AU 710236 B2	16-09-1999
		AU 1170297 A	01-08-1997
		AU 712539 B2	11-11-1999
		AU 1206697 A	01-08-1997
		AU 724404 B2	21-09-2000
		AU 1206797 A	01-08-1997
		CA 2240943 A1	17-07-1997
		CA 2242353 A1	17-07-1997
		CA 2242356 A1	17-07-1997
		CA 2242360 A1	17-07-1997
		CN 1211930 A	24-03-1999
		DE 69726599 D1	15-01-2004
		EP 1382293 A2	21-01-2004
		EP 0888082 A1	07-01-1999
		EP 0944350 A1	29-09-1999
		EP 0888150 A1	07-01-1999
		EP 0910429 A1	28-04-1999
		WO 9724983 A2	17-07-1997
		WO 9724981 A2	17-07-1997
		WO 9725101 A2	17-07-1997
		WO 9725098 A1	17-07-1997
		IL 125136 A	31-07-2003
		IL 125259 A	01-12-2002
		IL 125260 A	24-06-2003
		JP 2001502189 T	20-02-2001
		JP 2001502556 T	27-02-2001
		JP 2001509036 T	10-07-2001
		JP 2000502931 T	14-03-2000
		US 2002087089 A1	04-07-2002
		US 2002055674 A1	09-05-2002
		US 6171303 B1	09-01-2001
		US 6285898 B1	04-09-2001
		US 6363279 B1	26-03-2002
		US 2002045809 A1	18-04-2002
		AU 3356797 A	02-04-1998
		AU 3356897 A	02-04-1998
		AU 3356997 A	02-04-1998
		AU 3357197 A	02-04-1998
		AU 3357297 A	02-04-1998
		EP 1011793 A1	28-06-2000
		EP 0973581 A1	26-01-2000

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 04 25 0106

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29-03-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002032467 A1	14-03-2002	AU 5504301 A	12-11-2001
		EP 1284781 A2	26-02-2003
		WO 0182771 A2	08-11-2001
US 6055454 A	25-04-2000	NONE	
US 5908392 A	01-06-1999	NONE	
US 2003153953 A1	14-08-2003	US 2003153956 A1	14-08-2003
US 2004002741 A1	01-01-2004	NONE	